



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Michalopoulos and Bowen
Serial No. : 09/455,952 Examiner: Naff, D.
Filed : December 7, 1999 Group Art Unit:1651
For : A NOVEL LONG-TERM THREE-DIMENSIONAL
TISSUE CULTURE SYSTEM

#16
B9J
1/14/03

DECLARATION OF DR. GEORGE K. MICHALOPOULOS
AND WILLIAM C. BOWEN UNDER 37 C.F.R. §131

Assistant Commissioner for Patents
Washington, D.C. 20231

We, GEORGE K. MICHALOPOULOS AND WILLIAM C. BOWEN, do
declare:

1. We are co-inventors of the invention disclosed in the above-identified
application. A copy of each of our Curricula Vitae is attached herewith as Exhibit A and B.

2. The invention disclosed in the above identified application relates to
a novel tissue culture system that provides for the long term culture of proliferating
hepatocytes that retain hepatic function. Specifically, the invention relates to methods and
compositions for *ex vivo* culturing of hepatocytes and non-parenchymal cells on a matrix
coated with a molecule that promotes cell adhesion, proliferation or survival. The hepatic
cell culture system can be used to form bio-artificial livers for use in subjects having a
hepatic disorder.

3. Prior to January 1999, experiments were conducted to test whether hepatic cells and nonparenchymal cells obtained from liver tissue could be cultured together for hepatic reconstruction. The data presented below demonstrates successful culturing of hepatocytes and nonparenchymal cells that reproduce the hallmark structures of hepatic histological architecture while maintaining differentiation and the capacity to proliferate.

4. Rat hepatocytes were isolated from male Fischer 344 rats by an adaptation of Seglen's calcium two-step collagenase perfusion technique. Typically a 3% contamination with non-parenchymal cells is seen in this isolate. The freshly isolated hepatocytes were added to roller bottles (850 cm² surface). Each bottle contained 18.7×10^6 beads and 210×10^6 freshly isolated hepatocytes in 250 mL of HGM medium supplemented with HGF (20 ng/ml) and EGF (10 ng/ml). The bottles were rotated at a rate of 2.5 rotations per minute and kept in an incubator maintained at 37 °, saturated humidity, and 5% CO₂.

5. Exhibit C depicts thin sections of cells on beads in roller bottle cultures at day 15 after isolation, stained with toluidine blue. (A) The bead is seen as a hollow space in the center of the cell cluster. Gray material around the bead represents dense type-1 collagen deposition. The collagen surrounds and embeds connective-tissue-derived nonparenchymal cells. Cells with hepatocyte morphology surround the connective tissue core. (B) Similar as in A. The epithelial cells with hepatocyte morphology form an eccentric growth over a foundation of connective tissue cells. It is noteworthy that multiple microvilli have formed over the hepatocytes present on the surface.

6. The bead clusters containing cells were isolated from suspensions obtained from the roller bottle cultures. Enrichment for clusters was obtained by allowing for 2 minutes of unit gravity sedimentation. The bead and cell clusters were mixed with Matrigel (Collaborative Research). Bead clusters with cells were allowed to settle whereas beads without cells stayed mostly in suspension. The supernatant was aspirated leaving the clusters in the bottom of the tube. The process was repeated three times. Clusters suspended in medium were mixed with Matrigel at a volume ratio of 1:4 (medium plus beads:Matrigel). Approximately 50 to 100 bead clusters were randomly embedded in Matrigel.

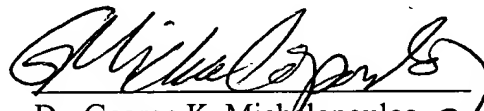
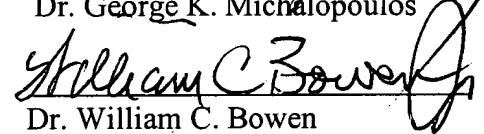
7. Exhibit D depicts cellular and matrix immunohistochemistry of cultures in Matrigel. Staining by immunoperoxidase. A, B, C and D show stains for desmin, collagen types I, III and IV respectively. Desmin-positive stellate cells are interspersed in close proximity to the hepatocytes. Collagen type III shows the strongest immunohistochemical response. Collagen type IV often formed basement membrane structures surrounding hepatocytes arranged in acinar or ductal configurations (arrow).

8. The data presented in Exhibits C and D demonstrates that hepatocytes in long term roller bottle cultures enter into a stable phenotype in terms of morphology and that in the presence of HGF, EGF and Matrigel the cultures are capable of undergoing complex morphogenetic transformations leading to the formation of ducts and plates. The growth in three dimensions forms ducts and sheets of mature hepatocytes surrounded by non-parenchymal cells. Proliferation and cell differentiation is very high in these cultures.

9. We hereby declare further that all statements made herein by our own knowledge are true and that all statements made on information and belief are believed to be true and further that we make these statements with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the united States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing therein.

Dated: 11-25-02

Dated: 11-25-02


Dr. George K. Michalopoulos

Dr. William C. Bowen

BIOGRAPHICAL

11/02

NAME:GEORGE MICHALOPOULOS, M.D., Ph.D.

BIRTH DATE: January 1, 1946

HOME ADDRESS: 35 Highland Road
Apartment 6207
Pittsburgh, PA 15102

BIRTH PLACE: Samos, Greece

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CITIZENSHIP: United States

BUSINESS ADDRESS:
Department of Pathology
University of Pittsburgh
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EDUCATION AND TRAINING

1963-70	Athens University Medical School, Athens, Greece, M.D.
1971-72	Department of Pathology, University of Wisconsin Medical School, Madison WI, Internship
1972-77	Department of Pathology, University of Wisconsin Medical School, Madison, WI, Residency
1972-77	Department of Oncology, University of Wisconsin, McArdle Laboratory for Cancer Research, Madison, WI, Ph.D.

APPOINTMENTS AND POSITIONS

1991-present	Professor and Chairman, Department of Pathology, University of Pittsburgh, Pittsburgh, PA
1995-1998	Interim Dean, School of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA
1987-91	Professor of Pathology, Duke University Medical Center, Durham, NC
1983-87	Associate Professor of Pathology, Department of Pathology, Duke University Medical Center, Durham, NC
1977-83	Assistant Professor of Pathology, Department of Pathology, Duke University Medical Center, Durham, NC

PROFESSIONAL CERTIFICATION AND LICENSURE

1969 Educational Council for Foreign Medical Graduates
1970 Medical Doctorate, Athens University Medical
1973 Wisconsin State Medical License Examination
1977 Anatomic Pathology Board Certification
1991 Pennsylvania Medical License (MD-044208-L)

MEMBERSHIPS IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

2001 Society of Regenerative Medicine and Stem Cell Biology, Member

1994-1995 University Association for Research and Education in Pathology (UAREP)
-Vice President (1994-1995)
-Member, Long-Range Planning Committee (1992-1994)

1993- Association of Molecular Pathology, (Founding Member, 1994)
American Society for Investigative Pathology (Council Member, 1994-1996)
Association of Pathology Chairmen (member, Research Committee)

1992- United States and Canadian Academy of Pathology, Inc.
American Association for Cancer Research
American Association of Pathologists
American Society for Cell Biology
American Association for the Study of Liver Disease
Association of Pathology Chairmen
American Society for Cell Biology
Pittsburgh Pathology Society
Allegheny County Medical Association
American Medical Association

PROFESSIONAL ACTIVITIES

Services

2002 Member, Advisory Board of the Division of Forensic Neuropathology
of Allegheny County

2001- Consultant, Pfizer Corporation.

2000- Liver Cell Transplant Corp., Consultant

1999-2002 American Society for Investigative Pathology, Meritorious Awards Committee

1999-2002 United States and Canadian Academy of Pathology, Castleman Award Committee

1997- Cytologix, Scientific Advisory Board

1997-2001 Snowbrand Pharmaceuticals, Inc. Consultant

1997-2001 Chemical Pathology Study Section, Division of Research Grants, NIH

1991 Chemical Industry Institute of Toxicology,
Scientific Advisory Board, Research Triangle Park, North Carolina

1990-1994	Upjohn Company, consultant
1986-present	Genetic Technology Incorporated, Scientific Advisory Board, member
1989-present	American Association of Pathologists Program Committee
1985	Chronic Hazard Advisory Panel on DEHP (sponsored by the National Academy of Sciences and the Consumer Products Safety Commission)
1985-1991	Metabolic Pathology Study Section, NIH
1980-1984	Pathology B Study Section, member, NIH
1977-1978	Travenol-Baxter Pharmaceutical company, consultant

University Activities

2001-	Member, University of Pittsburgh Physicians Compliance Committee
2001-	Member, Advisory Board for Pitt Med Magazine
1999-2001	Chair, University of Pittsburgh Physicians Policy Committee
2000	Member, Search Committee for Simmons Chair for Pulmonary Research
2000-	Member, Distinguished Faculty Committee, University of Pittsburgh
2000	Member, Committee on Standardization of University Reports
1999-00	Member, Pediatric University of Pittsburgh Practice Plan Committee
1997-99	Member, University of Pittsburgh Medical Center System Executive Committee
1996-99	Senior Vice Chancellor for Health Sciences' Planning and Budgeting Committee
1996-99	Member, Planning and Budgeting Committee of the President, UPMC Division
1996-	Member, Advisory Committee for the Center for Biomedical Informatics
1996-	Member, Pathology Graduate Training Program
1995-	Member, Executive Steering Committee
1991-98	Pathology Education and Research Foundation, Chairman of the Board
1991-97	Executive Planning Council, UPMC
1991-96	Transplant Council, UPMC
1991-96	Joint Hospital CEO/University Policy Review Group
1991-	Presbyterian University Hospital Medical Executive Committee
1991	Montefiore University Hospital Medical Executive Committee
1991-	Veterans Administration Dean's Committee
1991-	Clinical Chairmen, School of Medicine
1991-	Executive Committee, School of Medicine
1991-	Health Center Development Incorporated, Central Laboratory Services Incorporated, Central Imaging Services Incorporated Board
1986-1990	Member, Academic Council, Duke University Medical Center

Editorial Boards

1995-	Journal of Pathology
	Member, International Advisory Group
1994-96	Hepatology
1993-2000	Human Pathology
1992-	Laboratory Investigation
	Journal of the National Cancer Institute

**In Vitro Cellular and Developmental Biology
Journal of Cell Physiology**

1989-1992 Environmental Health Perspectives

Reviewer

Cancer Research
Molecular Pharmacology
Chemical Biological Interactions
Environmental Mutagenesis
American Journal of Pathology
Carcinogenesis
Cancer Letters
Laboratory Investigations
Experimental and Molecular Pathology
Science
Hepatology
J. Cell Physiology
Nature and Nature Medicine
Cell

FINANCIAL SUPPORT FOR RESEARCH

Funding Agency: NIH/NCI
Grant/Contract No.: CA35373
Title of Project: HGF, Liver Regeneration and Carcinogenesis
Principal Investigator: George Michalopoulos
Percent Effort: 25%
Entire Project Period: 1/1/97-12/31/05
Total Project Funding: Direct \$783,722
Current Project Funding: Direct \$161,577

Funding Agency: NIH/NCI
Grant Number: 1U01CA88110-01
Title of the project: Molecular Reclassification of prostatic cancer.
Principal Investigator: George Michalopoulos
Percent of Effort: 20%
Entire Project Period: 7/1/00-7/1/05
Direct annual: \$416,488

Maud Menten Research Endowment (as Chairman of the Department of Pathology)
Annual return: \$145,000
1995-present

PUBLICATIONS (Abstracts not included.)

1. Michalopoulos, G., Pitot, H.C. Primary culture of parenchymal liver cells on collagen membranes: Morphological and biochemical observations. *Exper. Cel. Res.* 94:70-78, 1975. (Note: Declared as a Citation Classic by Current Contents in 1990.)
2. Kitagawa, T., Michalopoulos, G., Pitot, H.C. Unscheduled DNA synthesis in cells from N-2 Fluorenylacetamide-induced hyperplastic nodules of rat liver maintained in a primary culture system. *Cancer Res.* 35:3682-3692, 1975.
3. Michalopoulos, G., Sattler, G.L., Pitot, H.C. Interaction of chemical carcinogens and drug metabolizing enzymes in primary cultures of hepatic cells from the rat. *Amer. J. Path.* 85:755-769, 1976.
4. Michalopoulos, G., Sattler, C.A., Sattler, G.L., Pitot, H.C. Cytochrome P450 induction by phenobarbital and 3-methylcholanthrene in primary cultures of hepatocytes. *Science* 193:907-909, 1976.
5. Michalopoulos, G., Sattler, G.L., Pitot, H.C. Maintenance of microsomal cytochromes b5 and P450 in primary cultures in parenchymal liver cells on collagen membranes. *Life Sci.* 18: 1139-1144, 1976.
6. Michalopoulos, G., Sattler, G.L., O'Connor, L., Pitot, H.C. Unscheduled DNA synthesis induced by procarcinogens in suspensions and cultures of hepatocytes on collagen membranes. *Cancer Res.* 38:1866-1871, 1978.
7. Michalopoulos, G.K., "Morphologic and biochemical studies of hepatocytes cultured on floating collagen membranes," Thesis for Doctor of Philosophy, University of Wisconsin, 1977.
8. Michalopoulos, G., Sattler, G.L., Pitot, H.C. Hormonal regulation and the effects of glucose tyrosine aminotransferase activity in adult rat hepatocytes cultured on floating collagen membranes. *Cancer Res.* 38:1550-1555, 1978.
9. Sattler, C.A., Michalopoulos, G., Sattler, G.L., Pitot, H.D. Ultrastructure of adult rat hepatocytes cultures on floating collagen membranes. *Cancer Res.* 38:1539-1549, 1978.
10. Michalopoulos, G., Russell, F., Biles, C. Primary cultures of hepatocytes on human fibroblasts. *In Vitro*, 15:796-806, 1979.
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15. Strom, S.C., Kligerman, A.D., Michalopoulos, G. Comparisons of the effects of chemical carcinogens in mixed cultures of rat hepatocytes and human fibroblasts. *Carcinogenesis* 2:709-715, 1981.
16. Michalopoulos, G., Strom, S.C., Kligerman, A.D., Irons, G., Novicki, D.L. Mutagenesis induced by procarcinogens at the hypoxanthine-guanine phosphoribosyl transferase locus of human fibroblasts cocultured with rat hepatocytes. *Cancer Res.* 41:1873-1878, 1981.
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25. Novicki, D.L., Strom, S.C., Jirtle, R.L., Michalopoulos, G. Cryopreservation of isolated rat hepatocytes. *In Vitro* 18:393-399, 1982.

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48. Jirtle, R.L., Michalopoulos, G. Enhancement of the clonability of adult parenchymal hepatocytes with the liver tumor promotor phenobarbital. *Carcinogenesis* 7:1813-1817, 1986.
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51. Marselos, M.A., Strom, S.C., Michalopoulos, G. Enhancement of aldehyde dehydrogenase activity in human and rat hepatocyte cultures by 3-methylcholanthrene. *Cell Biology and Toxicology* 2:257-269, 1986.
52. Cruise, J.L., Michalopoulos, G.K. Norepinephrine decreases EGF binding in primary rat hepatocyte cultures. *J. Cell Physiology* 127:39-44, 1986.
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56. Monteith, D.K., Novotny, A., Michalopoulos, G., Strom, S.C. Metabolism of Benzo(a)pyrene in primary cultures of human hepatocytes: Dose-Response over a four-log range. *Carcinogenesis* 8:983-988, 1987.
57. Michalopoulos, G., Peter Eckl, J.L., Cruise, D.L., Novicki, D.L., Jirtle, R.L. Models of rodent liver carcinogenesis. *Toxicology and Industrial Health* 3:119-128, 1987.
58. Eckl, P.M., Strom, S.C., Michalopoulos, G., Jirtle, R.L. Induction of sister chromatid exchanges in cultured adult rat hepatocytes by directly and indirectly acting mutagens/ carcinogens. *Carcinogenesis* 8:1077-1084, 1987.
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63. Marselos, M., Strom, S.C., Michalopoulos, G. Effect of phenobarbital and 3-methylcholanthrene on aldehyde dehydrogenase activity in cultures of HepG2 cells and normal human hepatocytes. *Chem. Biol. Interact.* 62:75-88, 1987.
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BOOKS, CHAPTERS, REVIEWS

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14. Michalopoulos, G.K., "Hepatocyte Growth Factor (HGF) and Its Receptor (Met) in Liver Regeneration, Neoplasia and Disease." Academic Press, edited by Randy L. Jirtle, Liver Regeneration and Carcinogenesis, 1995, pg. 27-49.
15. Zarnegar, R., DeFrances, M.C., and Michalopoulos, G.K. Hepatocyte growth factor: Its role in hepatic growth and pathobiology. The Liver: Biology and Pathobiology, Fourth Edition, edited by I.M. Arias, J.L. Boyer, F.V. Chisari, N. Fausto, D. Schachter and D.A. Shafritz. Lippincott Williams and Wilkins, Philadelphia, 2001. pg 611-629.

SEMINARS AND INVITED LECTURESHIPS

- 1976 Division of Experimental Pathology, National Cancer Institute, seminar
Department of Pathology, Northwestern University, seminar
- 1977 "Chemical Carcinogenesis Studies in Cell Cultures, American Association of Pathologists, F.A.S.E.B. Meeting, Session
- 1978 Environmental Protection Agency, Division of Genetic Toxicology, Seminar
Chemical Industry Institute of Toxicology, Seminar
"Liver: Quantitative Aspects of Structure and Function," Gstaadt, Switzerland
- 1979 Hercules Inc., Wilmington, Delaware, seminar
Chemical Industry Institute of Toxicology, seminar
Travenol-Baxter Company, Toxicology Division, seminar
- 1980 Department of Pathology, University of Alabama (Birmingham), seminar
Department of Pathology, University of Wisconsin, seminar "Effects of substrates on cell growth and differentiation," Tissue Culture Association Meeting, panel member
- 1981 New York Center for Blood Diseases, Section of Cell Biology, seminar
Workshop on Liver Cell Culture (sponsored by the American Tissue Culture Association) held at Alton Jones Cell Science Center, Lake Placid, New York, Co-director
- 1982 Workshop on Angiogenesis and Growth Regulation, Duke University, seminar
Department of Pathology, Cancer Center Seminar Series, University of Maryland, seminar
University of North Carolina in Chapel Hill, Cancer Center Seminar Series, seminar
Departments of Anatomy and Pathology, University of Wisconsin, Seminar
"Carcinogenesis of Aromatic Amines," National Center for Toxicology Research,

Jefferson, Arkansas

"Cell and Organ Cultures in the Investigation of Chemical Metabolism and Toxicity," American Tissue Culture Association Meeting

"Animal cell cultures: Control of cell growth," Symposium, SUNY Buffalo, NY

- 1983 Department of Pharmacology, Uniformed Services Medical School, Bethesda, MD, seminar
Cancer Center Seminar Series, Duke Medical Center, seminar
Rheumatology Seminar Series, Duke Medical Center, seminar
Hematology Seminar series, Duke University, seminar
Symposium on Liver Carcinogenesis, National Cancer Institute Human Studies,
Collaborative Group Meeting
- 1984 Department of Experimental Biology, University of Thessaloniki, Greece
Department of Anatomy, University of Patras, Greece
Minisymposium on Tumor Growth Factors, FASEB meeting, "Hepatocyte Cell Cultures,"
Tissue Culture Association Meeting
- 1985 Experimental Carcinogenesis, National Cancer Institute, seminar
Department of Surgery, University of Pittsburgh, seminar
Argonne National Laboratories, seminar
Department of Gastroenterology, University of Bari, Italy, seminar
Department of Pathology, University of Cincinnati, Ohio, seminar
"Bloodborne factors and liver regeneration: pursuit through in vitro studies,"
AAP President's Symposium on "Liver Regeneration." FASEB, 1985.
"Biological Mechanisms of Tumor Promotion," Association for Cancer
Research, Houston, TX, Co-Chairman, Poster Discussion Session
"Growth and differentiation of cells in culture," Symposium, Sendai, Japan.
"Hepatocyte Cultures," Kyoto, Japan.
- 1986 Department of Biology, University of Alabama, Tuscaloosa, AL, seminar
Department of Pathology, Case Western Reserve University, Cleveland, OH, seminar
Department of Pathology, Brown University, Providence, Rhode Island
"Regulation of Growth and Differentiation in Normal, Regenerative and Neoplastic
Hepatocytes," NIH
"Growth and Differentiation in Primary Hepatocyte Cultures," Cell Biology, SIRG meeting
- 1987 Department of Biochemistry, University of Tübingen, West Germany, seminar
Department of Biochemistry, University of Göttingen, West Germany, seminar
National Institute of Environmental Health Sciences (NIEHS), seminar
Genotoxic and Environmental Mutagen Society, Research Triangle Park, seminar
Department of Human Oncology, University of Wisconsin, Madison, WI, seminar
Minisymposium on Growth Factors, AACR meeting, seminar, director
"Regulation of Cell Proliferation and Differentiation: from Basic to Clinical
Implications," Ulm, West Germany

- 1988 "Mechanisms of Tumor Promotion," AACR meeting, co-director
Genetic Therapy, Inc., Washington, DC, seminar
FASEB Summer Research Conference on Neoplastic
Transformation of Liver Cells, Copper Mountain, CO, Aug. 14-19, Co-director
"Boundaries Between Promotion and Progression During Carcinogenesis,"
talk at "Human Carcinogenesis," Conference, Case Western Reserve University, Cleveland, OH,
Sept. 28-30, Moderator
Liver Regeneration, American Association for the Study of Liver Disease,
Chicago, IL, session speaker, Nov. 7-8, seminar
- 1989 Mitre Corporation, Washington, DC, seminar
Albert Einstein Medical School, Liver Center, seminar
"Pathobiology of Neoplasia," Medical College of Virginia, symposium
Clinical and Biological Aspects of Hepatic Regeneration Symposium, Bari, Italy,
June, Co-organizer
"Molecular Cell Biology of Liver Growth and Function," Fifth International Symposium on
Cellular Endocrinology, Lake Placid, NY, speaker
"Critical Target Genes in Chemical Carcinogenesis," NIEHS, speaker
"Mechanisms of Chemical Carcinogenesis," 5th International Sardinian Conference, speaker
Receptor Mechanisms Group, NIEHS, speaker
"Chemically induced cell proliferation: Implications for Risk Assessment,"
Austin, TX November 29, speaker
- 1990 Jefferson Medical College, Philadelphia, PA, seminar
"Nongenotoxic Carcinogens," Joint Panel on Environmental Mutagenesis and
Carcinogenesis U.S. - Japan Cooperative Medical Science Program, 17th
Joint Conference, February 5-7, Kailua-Kona, Hawaii, invited speaker
"Application of Molecular Biomarkers in Epidemiology," NIEHS, speaker
2nd International Symposium on Artificial Liver Support, Hannover, West Germany,
June 18-22, speaker
International Meeting on Liver Disease, Budapest, October 17-21, speaker
F.A.S.E.B. Summer Research Conference, Copper Mountain, CO, July 29-Aug. 3,
director and organizer
- 1991 "Endogenous growth factors and the stage of promotion," 75th Annual FASEB meeting,
Atlanta, GA, April 21-15.
"HGF, Liver Regeneration and Carcinogenesis," Genentech, Inc., San Francisco, CA, May 6,
seminar.
"Cell Growth Regulatory Effects of FK 506 and Rapamycin," FK 506 First
International Congress, Pittsburgh, PA, August 21-24, chaired session.
"Regulation of Liver Regeneration," British Society of Gastroenterology,

London, England, September 25-27, session organizer
 "HGF in Liver Regeneration and Carcinogenesis: Recent Developments,"
 Third Workshop on Mouse Liver Tumors, International Sciences Institute, Arlington, VA,
 October 29-30, speaker.
 "Hepatocyte Growth Factor," CIBA-Geigy, London, England, December, invited speaker.

- 1992 "Liver Regeneration," Regeneration Hepatique, French Association for Study of the Liver, Chamrousse, France, February 7-10, speaker.
 "Liver Growth Regulation in Regeneration and Carcinogenesis," Northwestern University, Chicago, IL, February 24, speaker.
 "Novel Growth Factors, FASEB Symposium, Anaheim, CA, April 5-9, session chairman.
 "Hepatocyte Proliferation in Liver Regeneration and Hepatitis," at the International Liver Forum, Tokyo, Japan, April 14-15, speaker.
 "Mechanism Controlling Liver Regeneration," Pennsylvania Association of Pathologists, Hershey, PA, May 1-2, speaker.
 "Hepatocyte Growth Factor in Liver Regeneration and Tumor Promotion," Genetic Toxicology Association, Wilmington, DE, May 12, speaker.
 "HGF and Liver Regeneration and Carcinogenesis," The Wellcome Research Laboratories, Research Triangle Park, NC, June 25, seminar.
 "HGF and Liver Regeneration and Carcinogenesis," Chemical Industry Institute of Toxicology, Research Triangle Park, NC, June 26, seminar.
 "Hepatic Regeneration and Carcinogenesis: Molecular and Cellular Pathways," FASEB Summer Conference, Snowmass, CO, July 12-17, Vice-Chairman, Conference Organizer.
 "Growth Factors in Liver Regeneration and Carcinogenesis," FASEB Meeting, Snowmass, CO, July 12-17, Session Organizer.
 "Hepatocyte Growth Factor (HGF) and Liver Regeneration," First United European Gastroenterology Week, Athens, Greece, September 25-30.
 "Molecular Diagnostics and Pathology: Opportunities and Challenges at the Departmental Level," Conference Organizer, UAREP Workshop on Pathology and Molecular Diagnostics: Issues of Structure and Organization, Bethesda, MD, October 28.
 "HGF and Liver Regeneration," American Association for the Study of Liver Diseases, State-of-the-Art lecture, Chicago, IL, November 2.
- 1993 "Growth factors and liver regeneration," Grand Rounds Johns Hopkins Hospital, Baltimore, MD January 27.
 "Regenerative factors and regulation in liver," Invited speaker for The 79th General Meeting of Japanese Society for Gastroenterology, Tokyo, Japan, March 29-31.
 "HGF and liver regeneration and morphogenesis," Invited speaker, Biannual Meeting on Liver Gene Expression, Cold Spring Harbor, NY, May 5-9.
 "Morphogenetic effects and mito-refractory state induced by hepatocyte growth factor and epidermal growth factor in hepatocytes in collagen gel," American Association for Cancer Research, Orlando, FL, May 19-22.
 "Role of hepatocyte factor and liver regeneration," Invited speaker, AASLD Single Topic Symposium, Liver Regeneration, Airline, VA, June 24-27.

"Tumor promotion: Hepatocyte Growth Factor (HGF)", Chaired session for Gordon Research Conference, Meriden, NH, July 5-9.

"Hepatocyte Growth Factor and liver growth regulation," Keynote Address Speaker, Joint Conference of the European Association for Cancer Research on Hepatocarcinogenesis, Heidelberg, Germany, September 12-15.

"Liver regeneration: Biological and clinical aspects," Kentucky Society of Pathologists, September 29.

"Cell lineages and growth regulation in fulminant hepatitis," Seminar, University of Kentucky, September 29.

"Hepatocyte Growth Factor" seminar, Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA, October 29.

"What is molecular diagnostics? Is there a home in Pathology?" Molecular Diagnostic Workshop, Universities Associated for Research and Education in Pathology, Inc., Bethesda, MD, November 12-14.

"The uptake and processing of hepatocyte growth factor (HGF) in normal and regenerating adult rat liver," American Association for the Study of Liver Diseases, Chicago, IL, November 4-7.

"HGF in liver regeneration and tumor promotion," presented at the Growth Factors and Tumor Promotion: Implications for Risk Assessment, 7th International Conference on Carcinogenesis and Risk Assessment, Austin, TX, December 1-4.

"Hepatocyte Growth Factor," seminar speaker at Thomas Jefferson Medical College, Philadelphia, PA, December 8.

"Hepatic Stem Cell Compartment: Activation and Lineage Commitment," conference participant, National Institutes of Health, National Cancer Institute, Bethesda, MD, December 9-10.

1994 "HGF as a growth regulator for normal and neoplastic hepatocytes," Molecular Aspects of Liver Carcinogenesis, NATO ASI meeting, Delphi, Greece, January 8-18.

"Current concepts on hepatocyte growth factor," seminar presented at Ohio State University, Columbus, OH February 6-7.

"HGF, carcinogenesis and liver regeneration," seminar given at Hershey Medical Center, Hershey, PA, February 24.

85th Annual Meeting of the American Association for Cancer Research, San Francisco, CA, April 10-13.

"Regulation of hepatocyte growth in liver regeneration and carcinogenesis," presentation at the American Society of Investigative Pathologists meeting, and co-chaired minisymposium Molecular mechanisms of growth control, and presented "Control mechanisms of liver regeneration," Anaheim, CA, April 24-28.

"HGF, carcinogenesis and liver regeneration," seminar presented at VA Medical Center, Memphis, TN, May 13.

"Hepatocyte growth factor in liver regeneration," presented at Case Western Reserve, Cleveland, OH, May 20.

"Liver regeneration: biological and clinical aspects," presented at Allegheny General Hospital, Pittsburgh, PA, May 25.

"HGF and the hepatic growth regulation," presented at Gastroenterology Week Freiburg 1994, Falk Symposium #78 Cytokines and the Liver, , Frieburg, Germany, June 15-16.

"Hepatic regeneration and carcinogenesis: molecular and cellular pathways," presenter and co-organizer for FASEB Summer Conference, Copper Mountain, CO, August 7-14.

"The role of hepatocyte growth factor in liver regeneration and carcinogenesis," presented at the 29th Annual Meeting of the European Association for the Study of Liver Disease, Athens, Greece, September 7-10.

Universities Associated for Research and Education in Pathology, Organizer, Molecular Pathology 1994 Workshop, Bethesda, MD, November 11-13.

"The In Vivo effects of hepatocyte growth factor and its receptor location in a normal liver and early hepatocellular carcinoma," American Association for the Study of Liver Disease, poster presentation, Chicago, IL November 14.

"Hepatocyte growth factor in liver growth biology," presented at Karolinska Institute, Huddinge, Sweden, November 7.

"Conversion of hepatocytes into hepatoblasts in the presence of HGF and EGF", Hepatic Stem Cell meeting, Bethesda, MD, December 8-9.

- 1995 "Hepatocyte growth factor (HGF) and transforming growth factor alpha (TGF) independently promote conversion of hepatocytes to hepatoblasts in long term in vitro conditions," poster presentation American Association for Cancer Research, Toronto, Ontario, Canada, March 18-22.

"Cellular biology of liver disease," seminar, Armed Forces Institute of Pathology, Washington, DC, April 7.

"Liver development, regeneration and carcinogenesis, poster presentation, ASIP Experimental Biology 95, Atlanta, GA, April 9-13.

"HGF in liver regeneration," seminar, Duke University Medical Center, Durham, NC, April 27.

"Molecular pathology of liver disease," seminar, Fourteenth Alexander Breslow Memorial lecture, Washington, DC, May 4.

"Cellular dynamics in liver regeneration and fulminant hepatitis," University of Florida, Resident Research Symposium, Keynote Speaker, Gainesville, FL, May 20.

"Human liver carcinogenesis," speaker, Aspen Cancer Conference, Aspen, CO, July 16-20.

- 1996 "Guides on future fulminant hepatic failure treatment based on cellular dynamics and HGF changes," International Conference for Apheresis, Co-chaired Session Plasmapheresis as a hepatic assist for acute hepatic failure and presented seminar Kyoto, Japan, April 7-10.

"HGF in control of hepatocyte growth and differentiation," seminar, Okayama University Medical School, Okayama, Japan, April 5.

Poster presentation at the American Association for Cancer Research, Washington, DC, April 20-24.

Poster presentations at the Joint Meeting of the ASBMB/ASIP/AAI, New Orleans, LS, June 2-6.

"Cellular and Molecular Mechanisms for Liver Growth Regulation," Co-chaired FASEB Summer Research Conference, Snowmass Village, CO, August 3-8.

"Hepatic Matrix, HGF, Hepatocyte Growth and Differentiation," International Congress on Hepatocytes - Applications in Cell Biology, Toxicology and Medicine, Speaker, Tübingen, Germany, September 25-28.

"Integration of signaling by growth factors in regeneration and carcinogenesis," XXI International Congress of the International Academy of Pathology, Budapest, Hungary, October 20-25.

"Hepatocyte growth factors," American Association for the Study of Liver Diseases, Workshop Moderator, Chicago, IL, November 8-12.

- 1997 "Hepatocyte growth control and differentiation," Department of Pharmacology Seminar Series, University of Pittsburgh Medical Center, February 14.
- "Liver regeneration: From Prometheus to HGF," Provost's Inaugural Lecture, University of Pittsburgh, February 26.
- "HGF, liver regeneration and hepatocyte differentiation," Division of Transplant Surgery, University of Pittsburgh Medical Center, March 3.
- "Liver, inflammatory and toxic injury, necrosis, fibrosis, regeneration, carcinogenesis," General Human Pathology Course, University of Pittsburgh, Lecture, March 13.
- "Mechanisms of control of hepatocyte proliferation," Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, March 31.
- "Hepatocyte Growth Regulation in Regeneration and Neoplasia," Department of Pathology, University of Alabama, AL, April 24.
- "HGF in liver regeneration and hepatocyte growth and differentiation," Regulation of Liver Gene Expression in Health and Disease meeting, Cold Spring Harbor, NY, April 30-May 1.
- "HGF, hepatocyte growth and differentiation," University of Montreal, Montreal, Quebec, Canada, May 14.
- "HGF, hepatocyte growth and differentiation," Johns Hopkins, Medical Center, Baltimore, MD, June 11-12.
- "Growth factors and the liver," Cytokine/Growth Factor/Peptides Seminar Series, Morgantown, WV, September 24.
- "Regulation of liver regeneration," Workshop, American Association for the Study of Liver Diseases, Chicago, IL, November 11.
- "Hepatocyte growth factor (HGF) and liver regeneration," New Frontiers in the Treatment of Liver Diseases, Padua, Italy, December 5-6.
- Hepatic Stem Cell Meeting, Washington, DC, Participant, December 11-12.
- 1998 "Growth factors in hepatic regeneration and cancer," Harvard Medical School, Boston, MA, Grand Rounds, January 12.
- "Hepatocyte growth factor (HGF) and liver regeneration," International Falk Workshop, Normal and Malignant Liver Cell Growth, Workshop, Halle, Germany, January 29-30.
- "Liver regeneration," Frederick Cancer Research and Development Center, Frederick, MD, February 5.
- "Liver Pathobiology," Experimental Biology Meeting, San Francisco, CA, Workshop, April 18-22.
- "HGF and hepatocyte growth and differentiation," Northwestern University, Chicago, IL., Seminar, May 4.

"Liver regeneration: Prometheus revisited," and "Comments on the future of academic pathology," Hershey Medical Center, Hershey, PA., Seminar, May 13.
 "Liver regeneration," 4th CGGH Symposium, Frontiers in Matrix Biology, Hiroshima, Japan, Keynote speaker, June 20-22.
 "Molecular mechanisms of liver regeneration," Federation of American Societies for Experimental Biology Summer Research Conference, Snowmass, CO, July 11-16.
 "How can Pathology drive the bandwagon?" Association of Pathology Chairman Workshop presentation, Boulder, CO, July 21-25.
 "HGF in liver regeneration and hepatocyte growth and differentiation," Integration of Hepatic Gene Regulation Symposium, Gottingen, Germany, October 30-31.
 "HGF in liver regeneration," 5th International Symposium of Hepatocellular Carcinoma, Taipei, Taiwan, Republic of Germany, November 29.
 "Growth and differentiation of hepatocytes in long-term cultures," Stem Cell meeting, Washington, DC, December 10-11.

- 1999 "Liver regeneration: Tissue engineering done by nature," Developmental Biology Symposium, Childrens Hospital Research Institute, Los Angeles, CA, February 4-7.
 "Liver regeneration after necrosis induced by allyl-alcohol and carbon tetrachloride," United States and Canadian Academy of Pathology, Inc., Poster Session San Francisco, CA, March 20-26.
 "HGF in liver regeneration and hepatocyte growth," Virginia Commonwealth University, Richmond, VA, May 7.
 "Liver mass homeostatis," 8th Biennial International Congress on Liver Development, Gene Regulation and Disease, Orvieto, Italy, June 2-6.
 "Funding for resident research - Pathways for resident research," Association of Pathology Chairs meeting, Boulder, CO, July 20-24.
 "HGF/SF and c-Met in Liver Development, Regeneration and Hepatocarcinosis," FASEB Summer Research Conference on Growth Factor Receptor Tyrosine Kinases in Mitogenesis, Morphogenesis, and Tumorigenesis, Snowmass Village, CO, July 31-August 5.
 "Regulation of hepatocyte growth in vivo and in vitro," 6th European Meeting on Hepatocarcinogenesis, Vienna, Austria, September 23-25.
 "Engineering of hepatic tissue," at the Tissue Engineering/Regenerative/Healing/Stem Cell Biology meeting, Pittsburgh, PA, October 3-5.
- 2000 "Liver regeneration," American Registry of Pathology, Washington, DC, January 11.
 "Hepatic regeneration," Chronic Hepatitis: New concepts of Pathogenesis, Diagnosis, and Treatment, Falk Workshop, Cologne, Germany, January 27-28.
 "Growth stimuli for hepatocytes in vivo and in vitro." Northwestern University Medical School, Chicago, IL, February 7.
 "Liver Regeneration," Seminar, UCLA, Los Angeles, CA, March 24, 2000.
 "Formation of morphogenic units of hepatic architecture by hepatocytes in culture," speaker for course "Liver Pathobiology: Liver Stem Cells," at American Society for Investigative Pathology Annual Meeting, San Diego, CA April 15.
 "Liver regeneration," Seminar, Mt. Sinai, New York, NY June 19-20.

"Panel discussion: Chanaging partners 10' vignettes from chairs who've been there," Pathology Treasures and Adventures: Introductory Remarks." Association of Pathology Chairs, Boulder, Co, July 26-29.

"Changing partners and creating partners/competitors –mergers and acquisitions and helpful/harmful spin offs," Association of Pathology Chairs meeting, Boulder, CO, July 26-29, 2000.

"Mechanisms of Liver Growth and Differentiation in Health and Diseases Session," FASEB Summer Research Conference, spoke on "Signaling Control of Liver Regeneration" Snowmass, CO, July 29-August 3.

"Liver Regeneration: Molecular Mechanisms of Growth Control,; Keynote Speaker, Fifth Oxford Workshop on Diabetes Research, Oxford, England, August 12-14.

"HGF in liver regeneration and hepatocyte differentiation," Seminar, Genentech, San Francisco, CA September 14.

"Liver regeneration," Workshop Moderator, American Association for the Society of Liver Disease, Dallas, TX, October 27-31, 2000.

2001 "Hepatocyte Growth Factor," Seminar, University of Miami, Miami, FL, February 7, 2001.

"WNT/ β -Catenin Pathway during Rat Liver Regeneration – A crucial Checkpoint Defined in Regulated Growth Enviroment," Abstract, American Association for Cancer Research, March 24-28, 2001, New Orleans, LS.

"Liver Pathobiology: Gene Therapy of Liver Disease," Session Leader, American Society for Investigative Pathology, March 31-April 1, 2001, Orlando, FL

"HGF in Liver Regeneration and Hepatocyte Differentiation," Seminar, University of Denver, Denver, CO, May 24, 2001.

"HGF and EGF in Hepatic Regeneration and Morphogenesis," Presentation, FASEB Summer Research Conference, August 4-9, 2001.

"Liver Regeneration," Workshop, American Association for the Study of Liver Disease, Dallas, TX, November 11, 2001.

"Liver Regeneration," Charlotte and Irving Shapiro Lecture, University of Pennsylvania, Philadelphia, PA, November 29, 2001.

2002 "Hepatocyte Growth Factor in Liver Regeneration and Hepatic Tissue Engineering,," Seminar, University of Florida, February 14, 2002.

"Hepatic Tissue in Culture," presentation at the Engineering Tissue Growth International Conference and Exposition, Pittsburgh, PA March 19-21, 2002.

"HGF, matrix and liver regeneration," Workshop presentation, American Society for Investigative Pathology, New Orleans, LA, April 20-24, 2002.

William C. Bowen, Jr.
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White Oak, PA 15131
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Education

January – May 1985

University of Pittsburgh – Pittsburgh, PA
Part-time student in Graduate School of Education
3 credits

September 1983 – May 1984

University of Pittsburgh – Pittsburgh, PA
Part-time student in Graduate School of Public Health
7 credits.

June 1977 - May 1981

The Pennsylvania State University
Bachelor of Science degree in Biology – May 1981

Relevant

Work Experience

December 1991 – Present

Research Specialist V, Department of Pathology
University of Pittsburgh School of Medicine, Department of Pathology - Pittsburgh, PA

April 1986 – December 1991

Senior Research Associate, Clinical Neuroendocrinology Program
Western Psychiatric Institute and Clinic – Pittsburgh, PA

Responsible for coordination and implementation of basic research on NIMH grant investigating the role of CRH in Major Depression. Duties included planning and performing experiments, development of procedures, supervision of two research associates, preparation of manuscripts for publication, review and presentation of data to Principal Investigators, inventory and ordering of supplies, and assisting in writing grants.

Familiar with tissue culture, electrophoresis, HPLC, RIA, ligand-receptor binding, iodination of peptides, liquid chromatography.

Experience in monoclonal and polyclonal antibody production, isolation of RNA and DNA, and RNA protection assay.

March 1983 – April 1986

Research Associate, Clinical Neuroendocrinology Program
Western Psychiatric Institute and Clinic – Pittsburgh, PA

Primarily performed RIAs for cortisol, growth hormone, prolactin, melatonin, and ACTH. Routinely performed computer calculations of data. Responsible for

development of RIAs for melatonin and dexamethasone.

November 1982 – February 1983

May 1982 – July 1982

June 1981 – September 1981

Laboratory Technician, Microbiology laboratory

McKeesport Hospital – McKeesport, PA

Responsible for logging in and primary planting of specimens for culture. Other duties included slide preparation and examination, operation of BAC-TEC automatic blood culture station, and patient billing on in-house computer.

PUBLICATIONS.

- 1: Michalopoulos GK, Bowen WC, Mule K, Lopez-Talavera JC, Mars W.
Hepatocytes undergo phenotypic transformation to biliary epithelium in organoid cultures.
Hepatology. 2002 Aug;36(2):278-83.
PMID: 12143035 [PubMed - indexed for MEDLINE]

- 2: Monga SP, Mars WM, Pediaditakis P, Bell A, Mule K, Bowen WC, Wang X, Zarnegar R, Michalopoulos GK.
Hepatocyte growth factor induces Wnt-independent nuclear translocation of beta-catenin after Met-beta-catenin dissociation in hepatocytes.
Cancer Res. 2002 Apr 1;62(7):2064-71.
PMID: 11929826 [PubMed - indexed for MEDLINE]

- 3: Michalopoulos GK, Bowen WC, Mule K, Stolz DB.
Histological organization in hepatocyte organoid cultures.
Am J Pathol. 2001 Nov;159(5):1877-87.
PMID: 11696448 [PubMed - indexed for MEDLINE]

- 4: Runge D, Runge DM, Daskalakis N, Lubecki KA, Bowen WC, Michalopoulos GK.
Matrix-mediated changes in the expression of HNF-4alpha isoforms and in DNA-binding activity of ARP-1 in primary cultures of rat hepatocytes.
Biochem Biophys Res Commun. 1999 Jun 16;259(3):651-5.
PMID: 10364473 [PubMed - indexed for MEDLINE]

- 5: Runge DM, Bowen WC, Katyal S, Runge D, Suski V, Michalopoulos GK.
Expression of the human hepatocyte growth factor cDNA in primary cultures of rat hepatocytes.
Biochem Biophys Res Commun. 1999 Apr 2;257(1):199-205.
PMID: 10092533 [PubMed - indexed for MEDLINE]

- 6: Michalopoulos GK, Bowen WC, Zajac VF, Beer-Stolz D, Watkins S, Kostrubsky V, Strom SC.
Morphogenetic events in mixed cultures of rat hepatocytes and nonparenchymal cells maintained in biological matrices in the presence of hepatocyte growth factor and epidermal growth factor.
Hepatology. 1999 Jan;29(1):90-100.
PMID: 9862855 [PubMed - indexed for MEDLINE]

- 7: Runge D, Runge DM, Drenning SD, Bowen WC Jr, Grandis JR, Michalopoulos GK.
Growth and differentiation of rat hepatocytes: changes in transcription factors HNF-3, HNF-4, STAT-3, and STAT-5.
Biochem Biophys Res Commun. 1998 Sep 29;250(3):762-8.
PMID: 9784420 [PubMed - indexed for MEDLINE]

- 8: Kim TH, Bowen WC, Stolz DB, Runge D, Mars WM, Michalopoulos GK.
Differential expression and distribution of focal adhesion and cell adhesion molecules in rat hepatocyte differentiation.
Exp Cell Res. 1998 Oct 10;244(1):93-104.
PMID: 9770353 [PubMed - indexed for MEDLINE]

- 9: Takeshita K, Bowen WC, Michalopoulos GK.
Three-dimensional culture of hepatocytes in a continuously flowing medium.
In Vitro Cell Dev Biol Anim. 1998 Jun;34(6):482-5.
PMID: 9661052 [PubMed - indexed for MEDLINE]

10: Miyazaki M, Mars WM, Runge D, Kim TH, Bowen WC, Michalopoulos GK.
Phenobarbital suppresses growth and accelerates restoration of differentiation
markers of primary culture rat hepatocytes in the chemically defined hepatocyte
growth medium containing hepatocyte growth factor and epidermal growth factor.
Exp Cell Res. 1998 Jun 15;241(2):445-57.
PMID: 9637786 [PubMed - indexed for MEDLINE]

11: Runge D, Runge DM, Bowen WC, Locker J, Michalopoulos GK.
Matrix induced re-differentiation of cultured rat hepatocytes and changes of
CCAAT/enhancer binding proteins.
Biol Chem. 1997 Aug;378(8):873-81.
PMID: 9377484 [PubMed - indexed for MEDLINE]

12: Block GD, Locker J, Bowen WC, Petersen BE, Katyal S, Strom SC, Riley T,
Howard TA, Michalopoulos GK.
Population expansion, clonal growth, and specific differentiation patterns in
primary cultures of hepatocytes induced by HGF/SF, EGF and TGF alpha in a
chemically defined (HGM) medium.
J Cell Biol. 1996 Mar;132(6):1133-49.
PMID: 8601590 [PubMed - indexed for MEDLINE]

13: Petersen B, Yee CJ, Bowen W, Zarnegar R, Michalopoulos GK.
Distinct morphological and mito-inhibitory effects induced by TGF-beta 1, HGF
and EGF on mouse, rat and human hepatocytes.
Cell Biol Toxicol. 1994 Aug;10(4):219-30.
PMID: 7895151 [PubMed - indexed for MEDLINE]

14: Michalopoulos GK, Bowen W, Nussler AK, Becich MJ, Howard TA.
Comparative analysis of mitogenic and morphogenic effects of HGF and EGF on rat
and human hepatocytes maintained in collagen gels.
J Cell Physiol. 1993 Sep;156(3):443-52.
PMID: 8360254 [PubMed - indexed for MEDLINE]

15: Yee CJ, DeFrances MC, Bell A, Bowen W, Petersen B, Michalopoulos GK,
Zarnegar R.
Expression and characterization of biologically active human hepatocyte growth
factor (HGF) by insect cells infected with HGF-recombinant baculovirus.
Biochemistry. 1993 Aug 10;32(31):7922-31.
PMID: 8347597 [PubMed - indexed for MEDLINE]

16: Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS,
Greenberger JS, Goff JP Science 1999 May 14;284(5417):1168-70.
Bone marrow as a potential source of hepatic oval cells.
Petersen BE, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS,
Greenberger JS, Goff JP

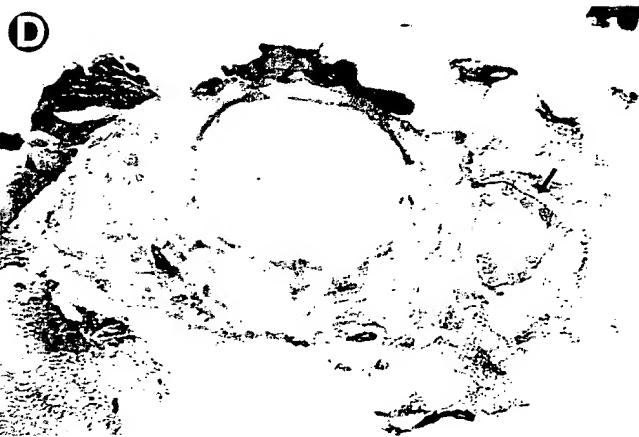
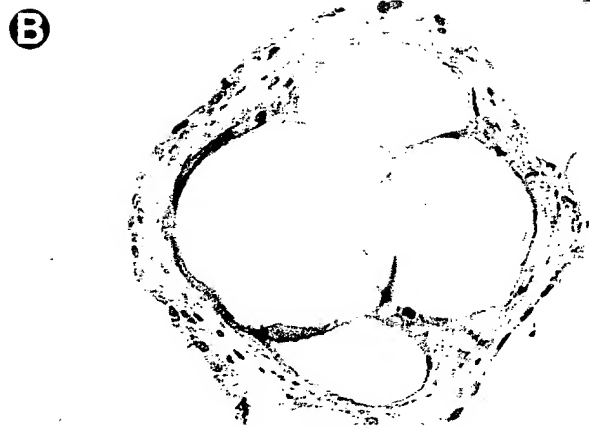


EXHIBIT D

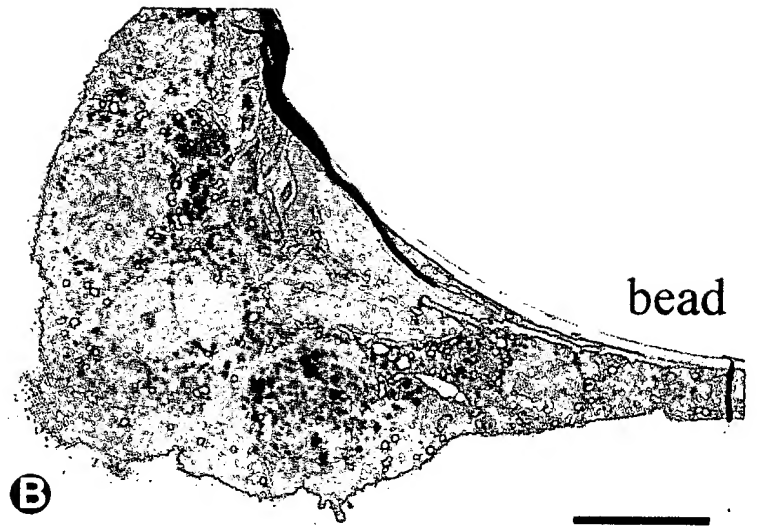
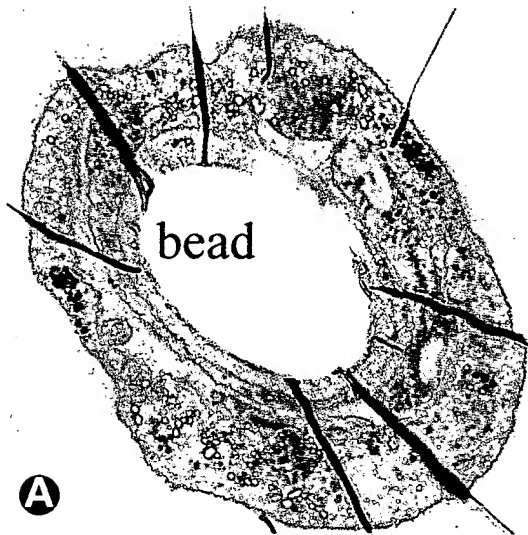


EXHIBIT C